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| 10/698,354 | 10/30/2003 | David James Rawson | PC25373A | 1622 |

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PHARMACIA CORPORATION
GLOBAL PATENT DEPARTMENT
POST OFFICE BOX 1027
ST. LOUIS, MO 63006

| EXAMINER | |
|---|---|
| ROYDS, LESLIE A | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/698,354 | RAWSON, DAVID JAMES | |
| | Examiner | Art Unit | |
| | Leslie A. Royds | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 January 2008 and 12 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15,18,20-22 and 27-29* is/are pending in the application.

4a) Of the above claim(s) *28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,18,20-22 and 27* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**Claims 15, 18, 20-22 and 27-29 are presented for examination.**

Applicant's Amendment filed January 7, 2008 has been received and entered into the present application. Applicant's Supplemental Amendment filed February 12, 2008 has also been received and entered into the present application. The Supplemental Amendment of February 12, 2008 was cited to correct a deficiency noted in the claim listing as discussed in the telephonic interview of February 12, 2008.

Claims 15, 18, 20-22 and 27-29 are pending. Claims 27-29 are newly added and claims 11-14, 16-17, 19, and 23-26 are cancelled.

Pursuant to the response filed February 24, 2006, Applicant elected, **with traverse,** the Invention of Group II (original claims 9-13), directed to compounds and pharmaceutical compositions or combinations thereof, and further elected the species of (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid as the compound to which examination was to be restricted if the generic claim was not found allowable. The election is herein reaffirmed and properly prompts the withdrawal of newly added claims 28-29 from consideration pursuant to 37 C.F.R. 1.142(b) as being directed to non-elected subject matter.

Accordingly, instant claims 15, 18, 20-22 and 27 are presently under examination. Claims 28-29 are withdrawn from consideration pursuant to 37 C.F.R. 1.142(b) as being directed to non-elected subject matter.

Applicant's arguments, filed January 7, 2008 and February 12, 2008, have been fully considered. Rejections and objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and objections are either reiterated or newly applied. They constitute the complete set of rejections and objections presently being applied to the instant application.

***Objection to the Claims (New Grounds of Objection)***

Claim 22 is objected to for referring to "A combination according to claim 21", which is in error, since claim 21 is directed to a "pharmaceutical composition", not a combination. Applicant may wish to consider amending the claim to now read ---A composition ~~combination~~ according to claim 21--- to obviate this objection. However, Applicant is notified that the adoption of such a suggestion does not necessarily equate to the obviation of any other objection and/or rejection set forth herein.

***Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement***

***(New Grounds of Rejection)***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 18, 20-22 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the compound (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid (compound of claim 18 and 27 and encompassed by the generic formula of claim 15), does not reasonably provide enablement for the use of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The presently claimed invention is directed to a compound of formula (Ib) (instant claim 15), specifically, the elected compound (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid (instant claims 18 and 27), and a pharmaceutical composition thereof that further comprises one or more pharmaceutically acceptable excipients, diluents or carriers (instant claim 20). The present claims further provide for a pharmaceutical composition comprising a compound of formula (Ib) (i.e., (2S, 4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid) or a pharmaceutically acceptable salt thereof and at least one other therapeutically active agent (instant claim 21). Instant claim 22 further specifies that the at least one other therapeutically active agent is a PDEV inhibitor selected from sildenafil, vardenafil, tadalafil, etc.

The instant claims are directed to the compound (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid, as well as the inclusion of such a compound into a pharmaceutical composition, along with one or more pharmaceutically acceptable excipients, diluents or carriers, into which may further be incorporated at least one other therapeutically active agent, such as a PDEV inhibitor, to be used for the treatment of various conditions, including epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, fibromyalgia, sleep disorders, osteoarthritis, rheumatoid arthritis, neuropathological disorders, visceral pain, functional bowel disorders (e.g., gastroesophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, inflammatory bowel diseases, such as Crohn's disease, ileitis, ulcerative colitis) and visceral pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis (p.7, Specification), which are conditions in which the alpha-2-delta receptor "is implicated" (p.9, Specification). However, the instant

specification as originally filed lacks adequate guidance, direction or discussion to apprise the skilled artisan how the claimed compound may be used to achieve the disclosed utilities for treating conditions wherein the alpha-2-delta receptor has been implicated, such as epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, fibromyalgia, sleep disorders, osteoarthritis, rheumatoid arthritis, neuropathological disorders, visceral pain, functional bowel disorders (e.g., gastroesophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, inflammatory bowel diseases, such as Crohn's disease, ileitis, ulcerative colitis) and visceral pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis (p.7, Specification), with at least a reasonable expectation of successfully achieving the treatment of the same. The instant specification fails to present any evidence, either in the form of data or scientifically sound reasoning, which would provide such a reasonable expectation that the claimed compounds would have been effective to treat the disclosed disorders. Though it is noted that Applicant need not necessarily demonstrate the precise manner in which the claimed therapeutic agent(s) ameliorate a particular disease state, such a mechanism must be elucidated in cases where Applicant relies upon a correlation between the particular activity of a compound (e.g., inhibition of a particular enzyme, binding to a particular receptor, etc.) and a reasonable expectation of efficacy in treating a particular disease.

In the instant case, Applicant relies upon the mechanism of action (i.e., interaction with the alpha-2-delta receptor) underlying the purported biological activity to establish that the genus of compounds instantly claimed would have been useful for treating conditions in which the alpha-2-delta receptor "is implicated". Notably, however, the purported effect and/or specific interaction of the instantly claimed compound with the alpha-2-delta receptor is never described within the four corners of the instant specification. In other words, though Applicant's inventive concept rests upon the correlation between the particular activity of the claimed compounds in interacting with the alpha-2-delta receptor to provide a reasonable expectation of efficacy in treating the disclosed disease(s) or disorder(s), the actual activity of

the instantly claimed compound and the receptor with which it is proposed to interact is not adequately described in the accompanying specification so as to enable the full scope of the instant claims.

Applicant provides various compounds and methods of synthesizing each, wherein Example 10 provides a method of synthesizing the instantly claimed compound, (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid, as well as numerous exemplary pharmaceutical formulations that comprise an active ingredient of the claimed compounds of the invention. Though Applicant's examples in this regard are duly noted, Applicant has failed to demonstrate that the instantly claimed compound [i.e., (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid] actually functions to achieve the disclosed therapeutic use of interacting with the alpha-2-delta receptor such that one of skill in the art would have thereby recognized its efficacious use in treating any one or more of the disclosed disease states. The specification fails to present either view a working or prophetic example(s) or a clear, scientifically sound explanation as to what, in fact, enables the interaction with the alpha-2-delta receptor such that the skilled artisan would have been imbued with at least a reasonable expectation of predictability of action in using the instantly claimed compound for use in treating any one or more of the disorders disclosed as being responsive to such an effect. Absent such guidance, the experimentation required to determine if there is any activity of any of the compounds in treating the disclosed disorders, and further, to determine, without needing to resort to random speculation, what therapeutic amounts would be available to even start testing for a therapeutic effect, would clearly be undue. Further, it is noted that, while the lack of a working embodiment cannot be the *sole* factor in determining enablement, the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter, in light of the unpredictable nature of the chemical and pharmaceutical arts and the limited direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole.

Although the instant specification states that the instantly claimed genus of compounds, which

encompasses the specifically elected compound [i.e., (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid], interact in some (unspecified) manner with the alpha-2-delta receptor to treat disorders in which the alpha-2-delta receptor "is implicated", the disclosure fails to provide any mechanistic discussion or provide any evidence or data, preclinical or otherwise, supporting the concept that the instantly claimed compound would, in fact, be effective to interact in such a way with the alpha-2-delta receptor so as to achieve the therapeutic treatment of the disclosed disorders. In the absence of such discussion or evidence, it is clear that the instant specification fails to support the enablement of the instantly claimed compounds in functioning to interact with the alpha-2-delta receptor such that the skilled artisan would have reasonably expected that the instantly claimed compound, effective in this manner, would have functioned to achieve the disclosed utility for treating conditions in which the alpha-2-delta receptor "is implicated" in a subject in need thereof.

As stated in MPEP §2164.04[R-1], "Doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation." In the instant case, the information that is missing is a clear correlation between the claimed compound and its efficacy in treating the disclosed conditions, either through specific evidence in the form of data demonstrating such a fact or at least a sound mechanistic correlation between the claimed compound, *its ability to function in such a manner* and the amenability of the claimed disease state to treatment using an agent capable of functioning in this manner. Though one of skill in the art might very well known how to treat a patient with the claimed compound once a diagnosis had been made of the claimed disorder (e.g., epilepsy, hypokinesia, etc.), it remains that the instant specification conspicuously fails to provide any guidance or direction in support of the *reasonable expectation of success* in actually effecting the treatment of the disclosed disorders using the instantly claimed compound in the absence of any evidence supporting the allegation that the claimed compound is, in fact, effective to achieve such a therapeutic objective, either by reduction to practice or at least by

elucidating the mechanism by which the claimed compound works and correlating such activity to therapeutic improvement of the disclosed disorders or diseases. In the absence of this information, the specification fails to provide adequate guidance and/or direction to one of skill in the art at the time of the invention that would have enabled such a person to practice the instantly claimed invention without having to resort to undue experimentation to determine how, in fact, one would achieve the instantly disclosed therapeutic objective(s).

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure and remarks that experimentation in this particular art is not at all uncommon, but that the experimentation required in order to practice the full scope of the invention would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added) Accordingly, in the absence of any adequate disclosure, direction or guidance as to how one would go about using the instantly claimed compound with a reasonable expectation of successfully treating the disclosed disorder(s), it remains that the pharmaceutical, chemical and medical arts are notoriously complex such that methods of use would have been sufficiently unpredictable to warrant the need for undue experimentation to actually practice the full scope of the invention as instantly claimed.

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor or scientist with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation or ability to make and use the full scope of the invention as instantly claimed, given the disclosure and supporting examples provided in the present specification and the state of the art at the time of the invention. In order to actually achieve the claimed invention, it is clear from the discussion above that the

skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the embodiments presently claimed.

***Conclusion***

Rejection of claims 15, 18, 20-22 and 27 is proper.

Claims 28-29 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

May 1, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614